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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,369	05/22/2001	Daniel Zagury	ZAGURY3A	9905

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EXAMINER	
PARKIN, JEFFREY S	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,369	ZAGURY ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4 and 5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4, and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Office Action

Status of the Claims

Acknowledgement is hereby made of receipt and entry of the communication filed 16 January, 2004. Claims 1, 2, 4, and 5 are pending in the instant application.

35 U.S.C. § 112, Second Paragraph

Claims 1, 2, and 4 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' arguments have been carefully considered but are not deemed to be persuasive. First, the claimed methodology has been amended to reference measuring anti-Tat antibody levels or anti-Tat antibody levels and p24 antigen levels. Perusal of the disclosure (i.e., pp 2 and 3, figure 4) appears to suggest that the most useful measurement was a combination of **both** anti-Tat antibody levels and p24 antigen levels. Thus, it is confusing as to how simply measuring anti-Tat antibody levels would allow the skilled artisan to make any meaningful predictions. Second, the methodology simply references "high" or "low" levels of antibody and p24 antigen production. This recitation is vague and indefinite because it fails to clearly set forth the parameters being measured. For instance, what constitutes high levels of p24 antigen (10, 20, 30, 40, 50, 60pg/ml)? What constitutes low levels of anti-Tat antibody production (0.2, 0.4, 0.6, 0.8 O.D. reading)? Applicants should amend the claim language to include those salient characteristics that would allow the skilled artisan to ascertain the metes and bounds of the patent protection desired.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C.

§ 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, and 4 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed toward methods for the determination of the prognosis of an HIV-infected individual and evaluating treatment regimens by measuring the level of anti-Tat antibodies or anti-Tat antibodies and p24 antigen levels.

As previously set forth, the legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The disclosure fails to provide a convincing correlation between measurement of the level of anti-Tat antibodies or anti-Tat antibodies and p24 antigen and the stage of disease progression. While it was reported that there was a statistically significant difference between nonprogressors (NP) and fast progressors (NP-P)

in terms of p24 antigen levels and anti-Tat antibody levels, nevertheless, this correlation is extremely weak. The values for the Tat antibody measurements were 0.39 for nonprogressors and 0.32 for progressors. The values for p24 antigen were 21.22 and 29.55 in nonprogressors and progressors, respectively. Moreover, the data set forth in Table 2 (p. 13) actually suggests that the vast majority (~73%) of progressors actually display low anti-Tat antibody levels, thereby reinforcing the concept that the correlation is quite weak. Thus, the skilled artisan would be reluctant to employ them in a meaningful prognostic protocol.

2) The prior art clearly teaches that Tat antibody profiles are not predictive of clinical outcome in HIV-infected patients. Reiss *et al.* (1991) examined the role of anti-Tat antibodies in disease progression in a large cohort and reported (see Abstract, p. 165) that "**antibody profiles** to nef, rev, **tat**, and protease **did not contribute to the prediction of outcome of infection.**" Franchini *et al.* (1987) also examined the association of anti-Tat antibodies with disease progression and concluded (see Abstract, p. 437) that "**No significant difference in antibody prevalence ...** to the 3'*orf*, *sor*, and ***tat*-III proteins (approximately 50%) was observed with regard to stage of the disease.**" Krone *et al.* (1988) also examined this issue and reported (see Abstract, p. 261) that "**Because of the low antigenicity of HIV-tat, antibodies to this regulatory protein are not a reliable marker for either early HIV-1 infection or subsequent disease progression.**" Thus, the prior art clearly contradicts the assertions made by applicants.

3) The prior art teaches that p24 antigen levels are not predictive of clinical outcome in HIV-infected patients. Donovan *et al.* (1996) examined the relevance of p24 antigen levels during AIDS-associated opportunistic infections and reported (see Abstract, p. 401) "**there was no consistent or significant change in p24 antigen levels** or CD4 cell counts **with either the onset of or recovery from**

an event." Pedersen *et al.* (1992) examined the significance of p24 antigenaemia in patients receiving zidovudine and acyclovir and observed (see Abstract, p. 821) that **"Disease progression occurred irrespective of whether p24-antigen levels declined during therapy. No association between p24-antigen responses to therapy and baseline disease stage, Karnofsky score or baseline CD4 count was detectable ...** Change in antigen level in response to antiviral therapy needs further investigation before it is used as a surrogate marker for clinical efficacy of antiviral therapy." Additional studies by Molina *et al.* (1994) also observed that **"None of these markers correlated with survival"** and that "Plasma viraemia and **ICD-p24 Ag,** while providing useful short-term markers of zidovudine antiviral activity *in vivo,* **do not correlate with disease progression in patients with advanced HIV infection."** Finally, Lafeuillade *et al.* (1994) concluded (see Abstract, p. 1028) that "In fact, **p24 antigenemia was correlated with only biological markers of immune activation ... The measurement of anti-p24 antibodies did not appear discriminative in our staging."** Thus, the skilled artisan would readily question the usefulness of p24 antigen measurements as a predictor of disease progression.

Therefore, when all the aforementioned factors are considered *in toto,* it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Applicants traverse and submit that the invention is fully enabled. Applicants argue that the disclosure demonstrates a clear inverse correlation between anti-Tat antibody levels and p24 antigen levels. Applicants are reminded that the claim language is not solely directed toward this observation. Moreover, applicants have not provided any evidence demonstrating that the skilled artisan could apply the claimed methodology with any confidence. As noted *supra,* nearly 75% of the progressor population actually

displayed low levels of anti-Tat antibody. Thus, if this assay were employed, it would clearly provide the wrong outcome the majority of the time. Moreover, several articles were cited clearly illustrating that anti-Tat antibody levels and p24 antigen levels are not tightly associated with disease progression. Applicants have failed to provide any scientific evidence or publications that rebut these findings. Therefore, the skilled artisan could not employ this assay with any meaningful confidence.

35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

Claim 5 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Rodman et al. (1992). Rodman and colleagues measured anti-Tat antibody levels in HIV-1-infected patients. This teaching does not disclose the measurement of anti-Tat antibody levels in patients that have been immunized with a putative Tat vaccine. Nevertheless, it clearly would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to measure anti-Tat antibody levels, as disclosed by Rodman and associates, in patients receiving a putative Tat vaccine, since this would allow one of ordinary skill in the art to assess the humoral immune response to such an immunogen.

Finality of Office Action

Applicants' amendment necessitated any and all new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL.** See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). **A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.**

Correspondence

Any inquiry concerning this communication should be directed to

Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 9:30 AM to 7:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, Laurie Scheiner or James Housel, can be reached at (571) 272-0910 or (571) 272-0902, respectively.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

02 April, 2004

MARK NAVARRO
PRIMARY EXAMINER